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Metabolic Changes Following Post-Hypoxic Complications in Newborns

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ABSTRACT

Background: To our knowledge, the role of neuron-astrocyte interaction in relation to Primary Astrocytes (PA) has never been revised to the moment. Here we have summarized many of the aspects that we think should be taken into account when studying PA, along with the newest advances in the field.

Objective: Given that the perinatal period is of particular importance for the developing brain, taking into account the continuous collaboration between astrocytes and neurons seems to be essential when studying PA pathogenic mechanisms and effects in the developing brain. As a fore said, the intricate relationship between these cell types plays a decisive role in the normal functioning of the developing CNS. Besides the crucial part they both play under healthy circumstances, there have been also great advances in identifying how this interaction works when brain insult occurs, influencing not only the development of brain injury in the perinatal period, but also the recovery.

Conclusion: We have extensively revised several advantages that each cell type has, compensating the disadvantages of the other one, the molecular and signaling pathways that could be activated under HI conditions and that enable crucial collaboration during energy failure.

Key Words: Asphyxia, Post-hypoxic changes, Hypoxia, Apgar scale, Periventricular hemorrhages, Placental disorders.

INTRODUCTION

The state of immunity at the time of birth largely determines the severity of the adaptive reactions of the newborn and, in addition, the immune system itself is one of the most important adaptation mechanisms of the organism and a powerful factor aimed at maintaining its antigenic homeostasis. An important, informative indicator of the state of the immune system of a newborn child in the early adaptation period is the level of cytokine production.^{1,2}

The need to assess the early postnatal adaptation of newborns who have undergone chronic or acute hypoxia is due to the peculiarities of the reactions of the fetal nervous tissue to hypoxic exposure. They relate to resistance to oxygen deficiency, excite toxic reactions, mechanisms of apoptosis, oxidative stress and the nature of secondary damage to brain tissue, caused in turn by the peculiarities of the metabolism of nervous tissue, incomplete myelination, immaturity of many

receptor systems and the morphofunctional organization of the blood-brain barrier. The consequences of the postponed asphyxia often remain underestimated, especially in the case of the birth of a child in a state of moderate asphyxia.^{3,4}

Modern instrumental diagnostic methods are quite laborious and are most often used already in the presence of neurological symptoms, which do not always have a clear and clear picture and their development may be delayed in time.

Determination of the clinical and immunological features of the period IV of early adaptation of full-term newborns who have undergone asphyxia of varying severity will improve perinatal outcomes and determine the reserve for reducing the incidence of children.^{5,6}

Establishing the cause of acute perinatal hypoxia in children causes great difficulties¹, because of which in childhood, in 20-30% of cases, they pass under other erroneous diagnoses.

Perinatal hypoxia, damaging the cyto-chemo-angio-architec-

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tonics of the nervous system, leads to multiple organ disorders affecting the adaptation of the body, the severity and prognosis of the course of the disease.^{1,2} Methods for the treatment of posthypoxic changes in the brain in newborns used in clinical practice, without taking into account the anatomical, physiological, age characteristics of the child's body.⁷ The aim of the study was to study the clinical features of the consequences of post-hypoxic changes in the brain in newborns.

MATERIALS AND METHODS

The neurosonographic signs of perinatal posthypoxic encephalopathy (PES) were studied using the method of ultrasound diagnostics, and clinical features of posthypoxic brain damage in newborns were revealed. Clinical features and results of brain examination in 240 newborns with posthypoxic brain injuries were studied. This pathology requires, in addition to clinical and neurological examination, echoencephalography, neurosonography, exhaustive research methods: computed tomography, magnetic resonance imaging, electroencephalography, rheoencephalography, Doppler sonography, cerebral angiography.

All children underwent a differentiated complex of conservative-restorative therapy, adapted to the characteristics of the child's age and the nuances of the morphological substrate in the acute and rehabilitation periods. Among 240 newborns, term babies prevailed in terms of gestational age, 132 (55%), premature babies accounted for 108 (45%). The study of the course of pregnancy revealed the presence of a pathological factor in 100% of cases - in 15% of cases, fetal pathology was established: chronic placental insufficiency, oligohydramnios, in 85% - maternal pathology: anemia, acute viral diseases, hypertension, chronic diseases (Figure 1).

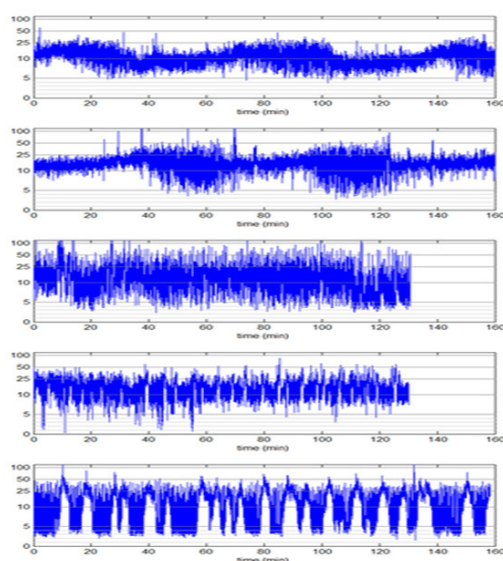


Figure 1: Maternal pathology: anemia, acute viral diseases, hypertension, chronic diseases

Chronic fetal hypoxia was detected in 40% of pregnant women. Among newborns: 65% of children (6-8 points on the Apgar scale) were in a state of mild asphyxia, children of moderate and severe severity were 35%, respectively.

Patients were admitted to the clinic within 1 hour to 9 days from the onset of the disease. Up to 60% of patients were admitted from non-core clinics - ordinary infectious diseases hospitals, after consulting neuropathologists. The reason for the late diagnosis is the lack of awareness of the medical staff about post-hypoxic changes in the brain in newborns, the complexity of diagnosis and the need for differentiation with a whole group of different conditions.^{6,7}

Most children in the family circle suffered from various cerebrovascular diseases and suffered cerebral strokes. In older children, background neurological diseases with elements of meteorological dependence were noted, occurring with an extensive group of subjective complaints, episodes of transient cerebral circulation disorders in the pre-stroke period.

Neurosonographic studies revealed:

Periventricular hemorrhages (PVH) - 96 (40%), with dilatation of the ventricular system (hydrocephalus) - 48 (20%), with ischemia of the subcortical nuclei - 24 (10%).

Table 1: Combined forms were identified: with Periventricular hemorrhages.

ischemia of the subcortical nuclei	38 (15.8%)
hydrocephalus and ischemia of the subcortical nuclei	34 (14.2%)
- diffuse changes in brain tissue	
edema of the cerebral parenchyma	36
periventricular (subcortical) cerebral ischemia	70

A specific feature of brain ultrasound of the acute period of PES in 240 infants was the predominance of periventricular ischemia of the brain tissue (mainly in premature infants), with intraventricular hemorrhages (mainly in full-term infants) and with cerebral edema (mainly in term infants). Periventricular cerebral ischemia is a sign of functional immaturity of the brain and was detected in premature infants and term infants (15%), which is a manifestation of cerebrovascular accident (Figure 2).

Edema and ischemia of the brain tissue in children with previous cerebral hypoxia first appeared during several days of life. The etiological factors of perinatal lesions of the nervous system in newborns were: asphyxia in 75% of children, 10% - infections, 8% - endocrine effects, and 7% - trauma. In the acute period of perinatal lesions of the nervous system, the following clinical syndromes most often occurred in newborns:

- with increased neuroreflex excitability - 70 children out of 206 (34%),
- children with the syndrome of general oppression were 2 times less common - 17.5%,
- 7 times less often - convulsive syndrome (4.8%).

In children with cerebral ischemia, the clinic was dominated by CNS excitation syndromes, signs of intracranial hypertension and CNS depression. Among newborns with intracranial hemorrhages in the acute period of PES, children with grade 2 IVH (grade 2-3 periventricular hemorrhages) predominated with signs of intracranial hypertension in the clinic, including in 30% of patients with the development of hydrocephalic syndrome (in premature infants), and in 25% of children - with symptoms of central nervous system depression (in full-term newborns). In 25% of children with IVH grade 2, convulsive syndrome was detected (only in full-term newborns). The fact of detecting clinical syndromes in some children with no ultrasound pathology of the brain in all periods of perinatal posthypoxic encephalopathy (mainly at the age of 1-3 months of life) indicates the presence of cerebral hemodynamic disorders both in newborns exposed to hypoxia and at a later age.

With the ratio of children with PVK of varying severity, mild forms of pathology were encountered - 55% of children with PVK of 1-2 degrees. The study of the timing of the appearance of other neurosonographic signs of PES revealed that dilation of the ventricular system of the brain and ischemia of the subcortical nuclei were first observed in patients mainly at the age of 1-3 months (48-20%), 2-4 times less often - the first day of life, even less often (24-10%) - at the age of 4-9 months of life. Combined forms of pathology (PVC and ischemia of the subcortical nuclei, hydrocephalus and ischemia of the subcortical nuclei) were first detected in children 1-3 months of age (55%), in 90 (37.5%) children - this pathology appeared at the age of 4 to 9 months, less often 18 (7.5%) - at the age of 6-30 days. The effectiveness of the proposed approach has been proven by a decrease in the neonatal period of cardiovascular disorders by 16.4% ($p = 0.034$); by the age of 1 year, cardiac arrhythmias by 12.3% ($p = 0.039$), sleep disorders by 20% ($p = 0.016$), hyperactive behavior, hyperexcitability by 18.4% ($p = 0.028$), psychomotor developmental delay by 14, 8% ($p = 0.045\%$).

Practical Recommendations

The obtained data on the high frequency and severity of functional cardiocerebral and metabolic disorders, which reduce the rate of postnatal adaptation, affecting the further development of children, in newborns who have undergone intrauterine hypoxia and born by surgery, should be individually taken into account when determining the indications and timing of surgical delivery.

In clinical practice, it is advisable to include in the first day of life in newborns who have undergone hypoxia, especially

those extracted by cesarean section, an extended protocol for echocardiographic examination of the heart with an assessment of diastolic function and mean pressure in the pulmonary artery to identify predictors of the development of dysadaptation-dilated cardiac remodeling (combination of mean pressure in pulmonary artery (MPAP) more than 25 mm Hg and biventricular diastolic dysfunction with E / A less than 0.9).

For newborns who have undergone intrauterine hypoxia, especially those born by surgery, it is recommended to conduct Holter ECG monitoring with the determination of heart rate variability indicators (term babies in the early neonatal period, and premature babies at the corrected age of 36-38 weeks) for early detection of neurovegetative dysfunction with the determination of predictors occurrence of hemodynamically significant cardiac arrhythmias (heart rate variability indices rMSSD more than 29 msec and pNN50 more than 1.5%).

Taking into account the main risk factors for the development of hypoxic-ischemic encephalopathy with sleep disorders in children who have undergone intrauterine hypoxia, especially those born by CS, we recommend monitoring cerebral blood flow in the early neonatal period (in the first 3 days - daily, then according to indications) in order to identify hypoperfusion of the brain against a background of high vascular tone ($RI > 0.8$) and a decrease in systolic and diastolic linear blood flow velocities.

DISCUSSION

Neurosonography is a valuable method for diagnosing post-hypoxic pathology of the brain in newborns, which allows, due to non-invasiveness, absence of radiation exposure, the possibility of multiple studies (monitoring), does not require special preparation of patients, to identify the timing of the appearance of neurosonographic signs of PES: PVC, hydrocephalus, ischemic changes in the brain tissue and subcortical nuclei, edema of the cerebral parenchyma and their combinations.^{5,6}

Prevention of perinatal encephalopathy consists in the possible minimization of risk factors during pregnancy, primarily in the refusal of the mother from the use of substances potentially dangerous for the child. If these conditions are met, perinatal encephalopathy cannot be ruled out completely. Timely treatment guarantees a complete recovery of 20-30% of children. The rest may have minor cerebral dysfunction, vegetative-vascular dystonia, temporary generalization of hydrocephalic syndrome. In the case of delayed diagnosis and treatment procedures, severe outcomes (cerebral palsy, epilepsy, persistent damage to the central nervous system and other brain diseases) are not excluded, requiring very serious long and expensive treatment.⁵

These data allow neonatologists, neuropathologists and pediatricians to more accurately assess the dynamics of post-hypoxic changes in the brain in newborns and children in the first three years of life, compensatory capabilities and adaptive reserves of the child's body.⁶ Among the identified antenatal and intranatal risk factors for the development of postnatal dysadaptation, including cardiocerebral disorders, in newborns who underwent intrauterine hypoxia, the most significant of them were identified in those born by surgery - hypertensive disorders

Table 2: Significant of Patient born by surgery hypertensive Disorder.

pregnancy and childbirth	(RR = 3.52 (95% CI 2.32-11.38), p = 0.000)
fetal distress	(RR = 3.16 (95% CI 1.76 - 9.71), p = 0.000)
premature placental abruption	(RR = 2.53 (95% CI 1.14 - 6.64), p = 0.000)
labor disorders	(RR = 2.07 (95% CI 1.82 - 5.23), p = 0.000)
intravenous anesthesia	(RR = 2.38 (95% CI 1.18 - 4.09) p = 0.000)
placental disorders	(RR = 1.90 (95% CI 1.61 - 2.24), p = 0.001)
combined somatic maternal pathology	(RR = 1.85 (95% CI 1.21 - 4.52), p = 0.001)

The catabolic orientation of metabolic processes in newborns extracted by caesarean section, in comparison with those born naturally, is associated with a large percentage of the loss of the initial body weight, a long period of its loss and a slower recovery rate. In these children, the severity of metabolic disorders is associated with the combined effect of negative factors of the antenatal and intrapartum periods, and impaired natural feeding. Among children who underwent hypoxia, those born by surgery are distinguished by a high representation (77.9% versus 63.7%, p = 0.000) and the severity of cardiac disorders (dilatation of cardiac cavities, diastolic dysfunction, pulmonary hypertension, rhythm disturbances) in the neonatal period and a long period of their reduction (3-6 months). The combination of high mean pulmonary artery pressure (more than 25 mm Hg) and biventricular diastolic dysfunction (E / A less than 0.9) is predictors of the development of dysadaptation-dilatational changes in the heart in the neonatal period in children undergoing hypoxia. The severity of autonomic imbalance with a deficit of sympathetic influences and an increase in heart rate variability rMSSD more than 29 msec and pNN50 more than 1.5% in newborns who have undergone intrauterine hypoxia, especially in those extracted by CS, creates the preconditions for arrhythmogenic mood of the myocardium and is a predictor of hemodynamic significant bradyarrhythmias.

Children born by surgery, in comparison with those born naturally in the early neonatal period, are distinguished by

a more significant disturbance of cerebral hemodynamics, which is associated with a higher frequency of delayed maturation of the bioelectrical activity of the brain and the formation of an unnecessarily intermittent EEG pattern (71.7% versus 59, 4%, p = 0.005). In the first year of life, these children often develop residual vascular disorders (84.5% versus 56.2%, p = 0.000), functional disorders of the central nervous system in the form of hyperactive behavior, hyperexcitability (47.9% versus 36.7%, p = 0.016), sleep disorders (47.2% versus 31.3%, p = 0.000). The significance of brain hypoperfusion in the early neonatal period with a resistance index (RI) of more than 0.8, systolic blood flow velocity (V max) less than 28 cm / sec and diastolic blood flow velocity (V min) less than 7.5 cm / sec in the development of hypoxic ischemic encephalopathy with sleep disorders. A consequence of renal hypoperfusion in the early neonatal period in children extracted by surgery is a higher incidence of ischemic nephropathy (37.2% versus 29.7%, p = 0.004). In children who underwent hypoxia and were born by surgery, in comparison with naturally born children, during the first half of their life, there was a slowed down dynamics of recovery of muscle-postural tone according to the INFANIB scale with the formation of transient disorders and a temporal delay of psychomotor development according to the CAT / CLAMS scale »By the coefficients of motor and cognitive development. By the age of 1 year, among children who underwent intrauterine hypoxia, those extracted by CS were diagnosed with a higher representation of functional disorders of the central nervous system (46-48%), morbidity of the gastrointestinal tract (32-38.2%) and skin (27.9%), cardiac arrhythmias (27.9%), due to the severity and duration of dysadaptation disorders in the neonatal period and slow recovery processes in the first year of life.

CONCLUSION

A comprehensive clinical and instrumental approach to the diagnosis of cardiocerebral dysfunction in children at risk in the early neonatal period made it possible to identify predictors of cardiocerebral disorders, to determine the frequency and scope of examination in the first year of life in order to timely carry out corrective measures and optimize the development of children in long-term periods.

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